IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Linda G. Cima, Edward W. Merrill, and Philip R. Kuhl

Serial No.: 08/398,555 Group Art Unit: 1811

Filed: March 3, 1995 Examiner: Jeffrey E. Russel

For: *CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES*

Assistant Commissioner of Patents
Washington, D.C. 20231

REPLY BRIEF

Sir:

The following comments are submitted in response to the Examiner's Answer mailed on January 12, 1998 in the above referenced patent application. It is believed that no fee is required for consideration of this Reply Brief. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 01-2507.

Appellants have appealed the final rejection of claims 1-32 in the Office Action mailed April 14, 1997 and maintained in the Advisory Actions mailed August 15, 1997 and September 16, 1997. A Notice of Appeal was mailed on September 24, 1997. Appellants' Brief was mailed on November 24, 1997.

(1) REAL PARTIES IN INTEREST

The real parties in interest are set forth in Appellants' Appeal Brief.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, the undersigned, or Appellants' assignee which directly affect, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-32 are pending and are on appeal. The text of each claim on appeal, as amended in the Amendment mailed January 23, 1997, is set forth in Appendix I to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The Amendment mailed January 23, 1997 was entered. Appellants hand delivered an Amendment on September 4, 1997 which was denied entry by the Examiner. On September 24, 1997, Appellants submitted a Petition Under 37 C.F.R. §1.181 to have the Amendment entered. On December 15, 1997, after Appellants' Appeal Brief was mailed, a decision was mailed denying the Petition Under 37 C.F.R. §1.181 to have the amendment of September 4, 1997 entered.

(5) SUMMARY OF THE INVENTION

The Summary of the Invention is set forth in Appellants' Appeal Brief.

(6) ISSUES ON APPEAL

The Issues on Appeal are set forth in Appellants' Appeal Brief.

(7) GROUPING OF CLAIMS

The grouping of claims is set forth in Appellants' Appeal Brief.

(8) ARGUMENTS

(a) The Claimed Invention

The claims are directed to compositions and methods for enhancing the rate of cell growth or for testing the effect of a compound on tissue. The compositions include a biocompatible substrate, biocompatible polymeric tethers, and growth effector molecules, wherein the molecules are covalently linked to one end of a tether and another end of the tether is covalently linked to the substrate. The growth effector molecules can freely interact with the cell but are not internalized by the cell. The growth effector molecules are attached at a concentration effective to enhance the rate of target cell growth.

(b) Rejections Under 35 U.S.C. §112

Claims 1-32 were rejected under 35 U.S.C. §112, second paragraph, because, it is alleged, the phrase "to enhance the rate of target cell growth" is indefinite. It was also argued that the term "polymer" in claims 5, 6, 21, and 22 is indefinite because it is not clear which polymer is meant. The test of whether the claims are indefinite is whether one skilled in the art can reasonably ascertain the scope of the claimed compositions and methods. *In re Moore*, 439 F.2d 1232, 169 U.S.P.Q. 236 (1971). A relational term does not render a claim indefinite if the specification provides a standard such that one skilled in the art can determine whether a particular product or process falls within the language of the claim. *Chisum on Patents*, §8.03[3] (1997), citing *Andrew Corp. v. Gabriel Electronics Inc.*, 847 F.2d 819, 821, 6 U.S.P.Q.2d 2010, 2012 (Fed. Cir. 1988). The purpose of the claimed

methods and compositions, as can be readily discerned from even a cursory reading of the application, is to enhance the rate of cell growth using substrates and growth effector molecules tethered to the substrates, as opposed to culturing the cells on a substrate in the presence of soluble molecules or molecules merely adsorbed to a substrate. Appellants submit that a person of skill in the art can readily determine what the term enhance means as used in the claims, by reference to the specification.

It would also be apparent to one of skill in the art that the term polymer in claims 5 and 21 refers to the biocompatible polymeric substrate that is referred to in claims 4 and 20. For one reason, claim 1 refers to "biocompatible synthetic polymeric tethers" and the further limitation of claim 5 to "synthetic polymers and natural polymers" would not make sense. The claims are definite because one of skill in the art can ascertain their scope.

(c) Rejections Under 35 U.S.C. §102(b)

i. Clapper Does Not Disclose Every Element Of The Claims

Claims 1-9, 13, 18-25, and 31 were rejected under 35 U.S.C. §102(b) as disclosed by Clapper. Appellants recognize that some of the molecules taught by Appellants as growth effectors are used by Clapper as cell adhesion factors. However, Clapper does not teach that they can be used to enhance the rate of cell growth as demonstrated and claimed by Appellants. The only way the molecules affect cell "growth" in Clapper's method is by increasing the number of cells attached to the substrate. Clapper does not demonstrate an increase in the rate of growth of attached cells. All of the measurements in Clapper relate to

the number of attached cells. Indeed, the entire focus of Clapper is to increase the number of attached cells. Appellants, on the other hand, demonstrate that the rate of growth of attached cells is enhanced. See Example 1 where the substrate having attached cells was washed to remove unattached cells and cell growth (of already attached cells) was measured by DNA synthesis.

The Examiner asserts that patentability must be based on claimed differences over the prior art. In this case, one claimed difference over the prior art is ". . . the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules." Clapper simply does not demonstrate this element. Nor, maintains the Appellants, can the compositions taught by Clapper achieve this cell growth rate enhancement because cells will adsorb to the positively charged tethers used by Clapper and the attached molecules will not be able to freely interact with the cells.

ii. EP '733 Does Not Disclose Every Element Of The Claims

Claims 1-7, 9, 10, 13, 18-21, 23, 25, 26, and 29-31 were rejected under 35 U.S.C. §102(b) as disclosed by EP '733 which discloses a carrier to which is immobilized a factor. The factor may be attached to the carrier through a linker or spacer that is preferably about 2 nm in length (page 3, line 53). Thus EP '733 discloses a composition similar to the adsorbed cell growth factor compositions to which Appellants compare their tethered compositions. The Examiner contends that there is no difference between growth effector

molecules immobilized by coupling and tethered growth effector molecules. Appellants, however, contend that their data demonstrates that these two types of compositions are not equivalent. See Figure 2 and the discussion at page 24, where it is demonstrated that Appellants' tethered growth effector molecules enhance cell growth as compared to adsorbed growth effector molecules.

The Examiner contends that the spacers used by EP '733 allow the attached molecules to freely change position and thus they are tethered. Appellants argue that this merely means that the molecules are not directly covalently coupled to the substrate. It does not mean that the molecules are tethered as defined and claimed by Appellants. Moreover, EP '733 does not disclose that the compositions taught therein enhance the rate of cell growth.

The Examiner again asserts that patentability must be based on claimed differences over the prior art. In this case, one claimed difference over the prior art is ". . . the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules." EP '733 simply does not demonstrate this element. Any inherency argument fails because the coupled molecules used by EP '733 will not achieve the degree of flexibility which Appellants have shown is necessary to achieve enhancement of cell growth. Moreover, polyethyleneimine, which is a synthetic polymer used in EP '733 to couple the molecules, is positively charged and, as discussed above with respect to Clapper, cells will adsorb to positively charged polymers and the attached molecules will not be able to freely interact with the cells.

iii. WO '616 Does Not Disclose Every Element Of The Claims

Claims 1-10, 12-26, 28, and 31 were rejected under 35 U.S.C. §102(b) as disclosed by WO '616. WO '616 does not teach how to tether growth effector molecules to alter cell growth. The Examiner correctly notes that a reference is not limited as teaching only what is taught in the examples. However, a reference with a general statement that something may be accomplished, without showing how it may be accomplished, cannot be an anticipating reference. *Chisum on Patents*, §3.04[1] (1997); *In re Paulsen*, 30 F.2d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994). Appellants disagree that the compositions taught by WO '616 inherently will enhance the rate of cell growth. WO '616 teaches the use of PEO which is a polymer that is commonly grafted to surfaces to inhibit cell adhesion. WO '616 does not teach how to achieve cell adhesion in the presence of a PEO tether so as to avoid rounding up and non-adherent cells. Appellants, on the other hand, show how to enhance the rate of cell growth by balancing use of polymeric water soluble tethers which do not bind to cells and the use of the proper amounts of tethered growth effector molecules.

(d) Rejections Under 35 U.S.C. §103

i. The Combination Of Herweck And Merrill '264 Does Not Render The Claims Obvious

Claims 1-9, 13-15, 18-25, and 31 were rejected under 35 U.S.C. §103 as obvious over Herweck in combination with Merrill '264. As argued in the Appeal Brief, there is no suggestion in either reference to incorporate the teaching of the other reference. Herweck

does not suggest that it would be advantageous to tether the factors to the substrate. Merrill '264 does not suggest using the star molecules for tethering growth effector molecules to a substrate. In fact, Merrill '264 teaches away from the claimed compositions and methods because it discloses, as the Examiner recognizes, that the PEO star molecules are non-thrombogenic, i.e., do not absorb proteins of the intrinsic clotting system or of the platelet membrane (see Merrill, column 1, lines 6-9). One of ordinary skill in the art would thus know that the use of PEO as a tether would tend to repel cells, and would thus believe that PEO would not allow contact of the attached growth effector molecules with the cells.

The Examiner argues that the motivation for combining references is because Merrill teaches that the star PEO molecules are non-thrombogenic. However, this is a property of PEO in general (see Merrill '264 column 1, lines 6-9) and not the star PEO molecules in particular. Therefore, there is no motivation to use star PEO or, more to the point, tethers. This is a classic case of hindsight. Appellants specifically teach in the application that Merrill's star PEO molecules can be used as tethers in the claimed compositions and, in fact, are preferred molecules. See page 7, lines 10-20 of the application.

Moreover, even if the teachings of the references are combined, the combination does not suggest the claimed compositions or methods because it does not suggest attaching growth effector molecules in a concentration and with tethers to a substrate so that cell growth is enhanced. Neither reference suggests how to tether growth effector molecules to alter cell growth. Even if one of skill in the art used PEO tethers in the device taught by

Herweck in order to prevent thrombogenesis, as suggested by the Examiner, there is no teaching in the references on how to do so to enhance cell growth.

With respect to the cell repellency of PEO, Appellants refer to *Rempp et al.*, Polymer Preprints, ACS (August 1991), a publication submitted with the amendment of July 14, 1997.

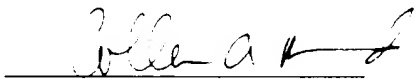
(9) SUMMARY

The cited prior art references do not teach or suggest compositions or methods for enhancing the rate of cell growth involving the use of a polymeric tether attached to a substrate that binds growth effector molecules so that the molecules cannot be internalized by the cell and the rate of growth of target cells is enhanced.

(10) CONCLUSION

For the foregoing reasons, Appellants submit that claims 1-32 are novel and non-obvious over the prior art and their allowance is earnestly solicited.

Respectfully submitted,



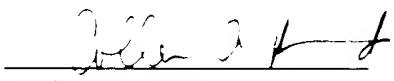
Collen A. Beard
Reg. No. 38,824

Date: March 12, 1998
Arnall Golden & Gregory, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, GA 30309-3450
(404) 873-8102
(404) 873-8103 fax

CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Date: March 12, 1998



Collen A. Beard

APPENDIX I

Claims as Pending in the Application

1. (once amended) A composition for stimulating the growth of eukaryotic cells comprising

a biocompatible solid substrate,

biocompatible synthetic polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules.

2. The composition of claim 1 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponge and shaped polymers.

3. The composition of claim 2 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

4. The composition of claim 1 wherein the biocompatible substrate is selected from the group consisting of glasses, metals and biocompatible polymers.

5. (once amended) The composition of claim 4 wherein the polymer is selected from the group consisting of synthetic polymers and natural polymers.

6. (once amended) The composition of claim 5 wherein the polymer is selected from the group consisting of proteins, polysaccharides, extracellular matrix proteins, polyesters, polycapralactone, polyhydroxybutyrate, polyanhydrides, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof.

7. The composition of claim 1 wherein the tether is a water soluble, biocompatible polymer.

8. The composition of claim 7 wherein the tether is selected from the group consisting of polyethylene oxide, carboxymethylcellulose, and starch.

9. (once amended) The composition of claim 1 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

10. The composition of claim 1 wherein the tether has a backbone length between 5 and 50,000 atoms.

11. The composition of claim 10 wherein the tether has a backbone length between 100 and 50,000 atoms.

12. The composition of claim 10 wherein the tether has a backbone length between 5 and 500 atoms.

13. (once amended) A method for growing eukaryotic cells comprising
bringing into contact the cells and a composition comprising
a biocompatible solid substrate,
biocompatible polymeric tethers, and
growth effector molecules,
wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and
maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow.

14. The method of claim 13 wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

18. The method of claim 13 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponges and shaped polymers.

19. The method of claim 18 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

20. The method of claim 13 wherein the biocompatible substrate is selected from the group consisting of glasses and biocompatible polymers.

21. The method of claim 20 wherein the polymer is selected from the group consisting of synthetic polymers and natural polymers.

22. The method of claim 21 wherein the polymer is selected from the group consisting of polylactic acid, polyglycolic acid, polyanhydrides, polyorthoesters, collagen, glycosaminoglycans, polyamino acids, and combinations thereof.

23. The method of claim 13 wherein the tether is a water soluble, biocompatible polymer.

24. The method of claim 23 wherein the tether is selected from the group consisting of polyethylene oxide, carboxymethylcellulose, and starch.

25. (once amended) The method of claim 13 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

26. The method of claim 13 wherein the tether has a backbone length between 5 and 50,000 atoms.

27. The method of claim 26 wherein the tether has a backbone length between 100 and 50,000 atoms.

28. The method of claim 13 wherein the tether has a backbone length between 5 and 500 atoms.

29. (once amended) The method of claim 13 wherein the cells are selected from the group consisting of parenchymal cells and stem cells.

30. The method of claim 29 wherein the cells are hepatocytes.

31. (once amended) A cell culture comprising
a biocompatible solid substrate,
biocompatible polymeric tethers,
growth effector molecules, and
growing cells,
wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules.

32. (once amended) A method of testing a compound for an effect on tissue comprising
bringing into contact the compound to be tested and a composition comprising
a biocompatible solid substrate,
biocompatible polymeric tethers,
growth effector molecules, and
growing cells,
wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;
incubating the compound and the composition under conditions promoting cell growth; and
observing the cells for any effect not observed in cells not brought into contact with the composition.

TABLE OF CONTENTS